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(54) Process for producing cyclohexylamino acids

(57) An industrial process is provided for producing optically active amino acids and derivatives having a cyclohexyl group or a substituted cyclohexyl group.

An amino acid, or derivative thereof, having a cyclohexyl group or a substituted cyclohexyl group is synthesized by hydrogenating an aromatic amino acid or derivative in the presence of a ruthenium catalyst. It is advisable that when an amino acid is an unprotected amino acid, the reaction is conducted in an aqueous solution containing a t least 1 equivalent of a base and that when an amino acid is a protected amino acid, the reaction is conducted in an aqueous solution or an alcohol solution.

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Description

The present invention relates to a process for producing optically active amino acid derivatives having a cyclohexyl group or a substituted cyclohexyl group which are important as intermediates of medications, especially intermediates of a renin inhibitor and the like.

A cyclohexyl group-containing amino acid is a constituent of a renin inhibitor described in WO 91/07430, EP 438311, EP 427939 and Japanese Laid-Open (Kokai) No. 9,162/1993. However, since this compound is a synthetic amino acid, it has aroused much interest from the pharmacological aspect.

A method of synthesizing a cyclohexyl group-containing amino acid is known per se. The known method synthesizes a racemic compound. Although this method uses an optically active compound as a starting material,the optical purity of the resulting amino acid is unclear, and this method is not said to include the specific production of an optically active amino acid which is a constituent of a renin inhibitor, a final compound of the present invention. Nor is it said to be an advantageous method because a solvent which can hardly be used industrially is employed and the yield is low.

Specific examples of the production of an amino acid having an optically active cyclohexyl group include the production of cyclohexylalanine by reducing L-phenylalanine in an acetic acid aqueous solution using a platinum oxide catalyst (J. Org. Chem., 1988, 53, 873, Tetrahedron, 1992, 48, 307), and the production of cyclohexylglycine by reducing (R)-phenylglycine in a carbon aqueous solution using a palladium hydroxide catalyst (Synth. Commun., 1978, 8, 345). However, in the former case, an optical purity is unclear. In the latter case, the yield is as low as between 24 and 66%, and cyclohexyl acetate is formed as a by-product at a ratio of from 27 to 68%. Further, the optical purity of the resulting cyclohexylglycine is between 66 and 84% ee, and this value is not satisfactory at all. Thus, these methods are not said to be industrially advantageous.

Incidentally, in the nuclear reduction of an aromatic hydrocarbon compound, the heat-reaction is generally conducted under hydrogen pressure in the presence of a catalyst such as rhodium, ruthenium, platinum or the like using an alcohol or the like as a solvent. With an unsubstituted aromatic hydrocarbon compound, the reaction proceeds relatively easily using a rhodium catalyst. However, with a hydrocarbon compound having a substituted aromatic ring, the reaction hardly proceeds owing to the influence of the resonance of the ring, or a side effect such as hydrogenolysis of a substituent or the like occurs. Thus, detailed studies on the reaction conditions are required in many cases (J. Org. Chem., 1958, 23, 276, Org. Syn., 1947, 27, 21).

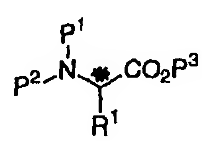
With respect to reduction of an aromatic ring of an aromatic compound having a substituent with an asymmetric carbon atom, it is reported that optically active mandelic acid is reduced in the presence of a rhodium catalyst (J. Org. Chem., 1962, 27, 2288). This document describes that the racemization is suppressed almost completely. However, product crystals having a purity of 92% ee are obtained from a starting material having a purity of 95% ee, and the racemization at a ratio of several percent is unavoidable. Regarding the racemization of mandelic acid, it is considered that the substituent in the benzyl position participates in the reaction as in (R)-phenylglycine described above to form a conjugated system relative to the benzyl position, with the result that the side reaction occurs with the racemization. Consequently, the nucleic reduction of optically active phenylglycine which is conducted while maintaining the optical purity thereof is considered to be especially difficult.

Meanwhile, it is reported that a ketone in a molecule of L-cyclohexylalanine derivatives is reduced in an alcohol solvent in the presence of a Raney nickel catalyst (J. Org. Chem., 1988, 53, 873). However, it is described that in spite of mild conditions, the racemization occurred at a ratio of 15% simultaneously with the reduction of the ketone moiety. It seems unlikely to avoid the racemization under some hydrogen reduction conditions of each moiety of an aromatic ring-containing amino acid.

It is desirable that embodiments of the present invention provide an industrial process for producing optically active amino acid derivatives having a cyclohexyl group or a substituted cyclohexyl group through the nuclear reduction of the corresponding amino acids at good yields without the racemization.

The present inventors have conducted investigations to solve the above-mentioned problems, and have consequently invented a process which may be used for producing amino acids having a cyclohexyl group or a substituted cyclohexyl group at good yields without the racemization by catalytically reducing aromatic amino acids in an aqueous solution containing a base, using a ruthenium catalyst even inthepresence of a base.

That is, the present invention is to provide a process for producing an amino acid represented by formula (I)

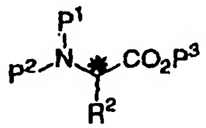


(I)

wherein

R^1 represents an optionally substituted cyclohexyl group having from 6 to 15 carbon atoms or an optionally substituted cyclohexylalkyl group having from 7 to 15 carbon atoms,
P^1 and P^2, independently from each other, represent a hydrogen atom or an amino-protecting group, or P^1 and P^2 together form a difunctional amino-protecting group,
P^3 represents a hydrogen atom or a carboxyl-protecting group, and
* represents an optically active carbon atom

or a derivative therefore; which process comprises hydrogenating an aromatic amino acid represented by formula (II)



(II)

wherein

R^2 represents an optionally substituted aryl group having from 6 to 15 carbon atoms or an optionally substituted aralkyl group having from 7 to 15 carbon atoms, and
P^1, P^2, P^3 and * are as defined above

or a derivative thereof, in the presence of a ruthenium catalyst in an aqueous or alcoholic solution containing a base. When P^1, P^2 and P^3 in formulas (I) and (II) are all hydrogen atoms, the reaction proceeds efficiently in an aqueous solution containing at least 1 equivalent of a base.

The aromatic amino acid represented by formula (II) or derivative thereof as used in the present invention may be natural or synthetic optically active amino acids.

Examples of the aromatic amino acid include L-phenylalanine, D-phenylalanine, D-phenylglycine, L-phenylglycine, L-tyrosine and D-tyrosine.

Examples of the aromatic amino acid derivatives include N-protected amino acids obtained by protecting the amino group of the above-mentioned aromatic amino acids, amino acid esters obtained by protecting the carboxyl group thereof, and N-protected amino acid esters obtained by protecting the amino group and the carboxyl group thereof. Any N-protecting group which is ordinarily used in peptide synthesis is available. Examples thereof include a tert-butoxycarbonyl group, an acetyl group, a formyl group, a trifluoroacetyl group and a phthaloyl group. Any carboxyl-protecting group which is ordinarily used in the peptide synthesis is available. Examples thereof include an ethyl ester group, a methyl ester group and a tert-butyl ester group. Further, examples of the N-protecting group include a benzyloxycarbonyl group and a dibenzyl group. Examples of the carboxyl-protecting group include a dibenzyl ester group. Thus, these protecting groups which are deprotected through reduction can also be used. In this case, a deprotected product is provided.

The protected aromatic amino acid derivatives can easily be synthesized by an ordinary production method.

When the starting material is an unprotected amino acid, the reaction may easily proceed through stirring in an aqueous solution containing at least 1 equivalent of a base under hydrogen pressure in the presence of a ruthenium catalyst.

On the other hand, when the starting material is an N-protected amino acid, the reaction may easily proceed through stirring in an aqueous solution or an alcohol solution (eg a solution in ethanol) at a hydrogen pressure in the presence of a ruthenium catalyst. In this case, the reaction also preferably proceeds in at least 1 equivalent of a base.

Specifically, from 1- to 10-% ruthenium on carbon may be used as a ruthenium catalyst in an amount of from 0.001 to 0.1 equivalents based on the amount of the starting amino acid, and a hydrogen pressure of from 1 to 100 atm may preferably be employed.

Examples of the base include sodium hydroxide, potassium hydroxide and ammonia. The amount of the base is between 1 and 10 equivalents, preferably between 1 and 2 equivalents. The concentration of the base is, for example, between 0.1 and 2.0 N.

Preferred reaction temperature is between room temperature and 250°C, particularly preferably between 40 and 150°C. The reaction may be completed in from 1 to 24 hours.

The reaction solution may be filtered to remove the catalyst. Subsequently, eg if the reaction was conducted in a basic aqueous solution, the residue may be neutralized or acidified to precipitate the product in the form of a free substance or a salt. Thus, the final product can easily be isolated and purified.

Examples

The present invention is illustrated more specifically by referring to the following Examples. However, the present invention is not limited thereto. The temperature is indicated in terms of a centigrade temperature unless otherwise indicated. Proton nucleic magnetic resonance spectra were recorded on a varian 300 MHz spectrometer; chemical shift (δ) is shown below in terms of ppm. The analysis of N-unprotected amino acid optical isomers was conducted using a Shimadzu Optical Analysis Gas Chromatography DLAA-1 (column: Chirasil Val/ASA) System. The isomers were determined from areas (%) on a chart given by automatic derivatization into N-trifluoroacetyl and isopropyl esters and analysis thereof.

Example 1

Production of L-cyclohexylalanine·hydrochloride:

L-phenylalanine (2.010 g, 12.2 mmols) and 105.1 mg (0.05 mmols) of 5-% ruthenium on active carbon as a catalyst were dissolved in 15 ml of a 1-N sodium hydroxide aqueous solution, and the solution was stirred at 60°C and a hydrogen pressure of 30 kg/cm^2 for 4.5 hours. The analysis of the reaction solution through HPLC revealed that the reduction proceeded quantitatively. With respect to the optical purity at this time, the area ratio was found to be L:D = 99.5 : 0.5 as a result of the analysis through optical analysis gas chromatography. After the completion of the reaction, the reaction mixture was filtered through Celite to remove the ruthenium on active carbon as a catalyst. Thus, a sodium hydroxide solution of cyclohexylalanine was obtained. The resulting filtrate was concentrated to approximately 1/3 of the original volume under reduced pressure. Then, 11 ml (66 mmols) of a 6-N hydrochloric acid aqueous solution and 12.8 ml of water were added to the residue. The mixture was dissolved while being heat-stirred, and then precipitated through cooling to give 1.681 g (98.3% by weight, 7.96 mmols) of L-cyclohexylalanine hydrochloride in a yield of 65.2%.

As a result of the analysis through optical analysis gas chromatography, the area ratio was found to be L:D = 99.7 : 0.3.

1H-NMR(D2O) δ:0.88-1.08(m, 2H) 1.15-1.34(m,3H) 1.34-1.52(m, 1H) 1.58-1.86(m,7H) 3.89(dd,1H)

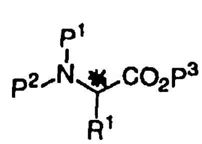
Example 2

Production of (S) -cyclohexylglycine·hydrochloride:

(S)-phenylglycine (1.966 g, 13.0 mmols) and 106.6 mg (0.05 mmols) of 5-% ruthenium on active carbon as a catalyst were dissolved in 15 ml of a 1-N sodium hydroxide aqueous solution. The solution was then stirred at 60°C and a hydrogen pressure of 30 kg/cm^2 for 5 hours. The analysis of the reaction solution through HPLC revealed that the reduction proceeded quantitatively. At this time, as a result of the analysis through optical analysis gas chromatography, the area ratio was found to be S:R = 99.2 : 0.8. After the completion of the reaction, the reaction mixture was filtered through a Celite to remove the ruthenium on active carbon as a catalyst and obtain a sodium hydroxide solution of cyclohexylglycine. The resulting filtrate was concentrated to approximately 1/3 of the original volume under reduced pressure, and 11.2 ml (67.2 mmols) of a 6-N hydrochloric acid aqueous solution and 1 ml of water were added to the residue. The mixture was dissolved while being heat-stirred, and was precipitated through cooling to give 1.678 g (100% by weight, 8.7 mmols) of (S)-cyclohexylglycine·hydrochloride in a yield of 65.4%. As a result of analysis through optical analysis gas chromatography, the area ratio was found to be S = > 99.98 (R = < 0.02).
1H-NMR(D2O) δ:1.05-1.37(m,5H) 1.62-1.81(m,5H) 1.93-2.03(m,1 H) 3.82(d,1H)

Claims

1. A process for producing an amino acid represented by formula (I)

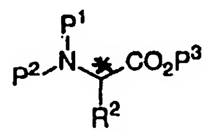


(I)

wherein

R^1 represents an optionally substituted cyclohexyl group having from 6 to 15 carbon atoms, or an optionally substituted cyclohexylalkyl group having from 7 to 15 carbon atoms
P^1 and P^2, independently from each other, represent a hydrogen atom or an amino-protecting group, or P^1 and P^2 together form a difunctional amino-protecting group,
P^3 represents a hydrogen atom or a carboxyl-protecting group, and
* represents an optically active carbon atom;

or a derivative thereof; which process comprises hydrogenating an aromatic amino acid represented by formula (II)



(II)

wherein:

R^2 represents an optionally substituted aryl group having from 6 to 15 carbon atoms or an optionally substituted aralkyl group having from 7 to 15 carbon atoms, and
P^1, P^2, P^3 and * are as defined above

or a derivative therefore; in the presence of a ruthenium catalyst in an aqueous or alcoholic solution containing a base.

2. The process of claim 1, wherein P^3 in formulas (I) and (II) is hydrogen atom.

3. The process of claim 1 or claim 2, wherein P^1, P^2 and P^3 in formulas (I) and (II) are all hydrogen atoms.

4. The process of any one of the preceding claims, wherein the reaction is conducted in an aqueous solution containing at least 1 equivalent of a base.

5. The process of any one of claims 1 to 4, wherein the optically active carbon atom in formulas (I) and (II) has an S-configuration.

6. The process of any one of claims 1 to 4, wherein the optically active carbon atom in formulas (I) and (II) has an R- configuration.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 30 5973

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
A	US 4 048 222 A (SAITO TSUYOSHI ET AL) 13 September 1977 * the whole document * ---	1,4	C07C227/16 C07C229/28
A	DATABASE WPI Section Ch, Week 7723 Derwent Publications Ltd., London, GB; Class A41, AN 77-41256Y XP002042036 & SU 526 616 A (AS LITH BIOCHEM INS ET AL.) , 7 December 1976 * abstract * ---	1	
A	GB 1 290 923 A (ICI LTD) * the whole document * ---	1	
A,D	PAUL FRANCIS SCHUDA ET AL.: JOURNAL OF ORGANIC CHEMISTRY., vol. 53, no. 4, 1988, EASTON US, pages 873-875, XP002042034 * page 874 * ---	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A,D	M. TAMURA ET AL.: SYNTHETIC COMMUNICATIONS, vol. 8, no. 5, 1978, pages 345-351, XP002042035 * page 346, line 12 - page 349 * -----	1	C07C

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	30 September 1997	Rufet, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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